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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/901,910	07/11/2001	Haodong Li	PF126P2	7856

22195 7590 07/29/2003

HUMAN GENOME SCIENCES INC
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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	12

DATE MAILED: 07/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/901,910	LI ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,24,25 and 27-54* is/are pending in the application.

4a) Of the above claim(s) *15,24,25 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 28-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to the Election filed June 16, 2003, in Paper No. 10.

Claims 1-15 and 24, 25 and 27-54 are pending in the instant application.

Claims 16-23 and 26 have been canceled. Claims 6 and 14 have been amended. New claims 28-52 are acknowledged. Claims 15, 24, 25, and 27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Claims 1-14 and 28-52 have been examined to the extent they read on the elected subject matter.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-14), in Paper No. 10 is acknowledged. The traversal is on the ground(s) that the restriction is improper because a search and examination of all groups would not entail a "serious burden" on the Examiner. Further, Applicant argues that a search of the polynucleotide claims would provide useful information for the claims in the other related groups, and therefore would not place an undue burden on the Examiner. More specifically, Applicants argue that a search of CTGF-2 polynucleotides would inherently provide relevant information for CTGF-2 polypeptides and antibodies. Furthermore, Applicants argue that the information about CTGF-2 polynucleotides, polypeptides and antibodies would reveal relevant information pertaining to methods of using CTGF-2 polynucleotides, polypeptides and antibodies. Applicants argue that a search of Group I (CTGF-

2 polynucleotides) would overlap with a search of Groups II-V (methods of using the CTGF-2 polynucleotides, polypeptides and antibodies).

This is not found persuasive because, as argued in the restriction requirement (Paper No. 9), a search of CTGF-2 polynucleotides would not provide relevant information for CTGF-2 polypeptides and antibodies since these are different molecules with different chemical and physical structures so that independent searches of the prior art would be required for each, which would constitute a serious burden on the Examiner. As further argued, the information about methods of using CTGF-2 polynucleotides would not reveal relevant information pertaining to methods of using CTGF-2 polypeptides and antibodies, since these are different molecules with different chemical and physical structures so that independent searches of the prior art would be required for each, which would constitute a serious burden on the Examiner. As further argued in the restriction requirement, methods of using CTGF-2 polynucleotides, polypeptides and antibodies are unrelated methods, which differ in reagents and/or dosages and/or schedules used, response variables, and criteria for success. Thus, these methods are materially distinct and independent searches of the prior art would be required for each, which would constitute a serious burden on the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

Priority

The priority information in the first line of the Specification is acknowledged. Upon review of the specifications of the parent applications and comparison with the specification of

the present application, it is determined that the specifications of parent applications 08/459,101, now U.S. Patent 5,945,300 and PCT/US94/07736, now International Publication No. WO96/01896 are *not* enabling for the method of stimulating angiogenesis in a mammal comprising the administration of a polynucleotide encoding CTGF-2. The 08/459,101 and PCT/US94/07736 applications do not provide any guidance or examples, prophetic or working, regarding the elected inventions drawn to a method of stimulating angiogenesis in a mammal comprising the administration of a polynucleotide encoding CTGF-2. Accordingly, the presently claimed invention has priority to U.S. Patent Application Serial No. 09/348,815, now U.S. Patent 6.534,630, filed July 8, 1999.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14 and 28-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-14 and 28-52 are indefinite because they recite the term "derivative". The term "derivative" is not defined by the claim and the specification does not provide a standard for ascertaining the requisite degree of a derivative of a polynucleotide encoding CTGF-2 and one of skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention. One of skill in the art would not be able to envision the structure of a derivative of a

polynucleotide encoding CTGF-2 (see also 35 U.S.C. 112, first paragraph rejection below against claims 1-14 and 28-52 for written description). For example, would the derivative of a polynucleotide encoding CTGF-2 be biologically active? Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 and 28-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, pages 1099-111 (also available at www.uspto.gov).

Claims 1-14 and 28-52 are drawn to a method of stimulating angiogenesis in a mammal, comprising administering a polynucleotide encoding CTGF-2, an active fragment or derivative thereof.

When the claims are analyzed in light of the specification, instant invention encompasses a polynucleotide encoding CTGF-2, an active fragment or derivative thereof. However, the specification discloses only SEQ ID NO: 2 and SEQ ID NO: 7 that encode a polypeptide disclosed as CTGF-2. In analyzing whether the written description requirement is met for genus

claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, SEQ ID NOs: 2 and 7 are the only sequences whose complete structure is disclosed. The specification does not provide any disclosure as to what would have been the active fragment or derivative of a polynucleotide encoding CTGF-2, other than SEQ ID NO: 7 (see also 35 U.S.C. 112, second paragraph rejection above against claims 1-14 and 28-52 for indefiniteness).

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, only SEQ ID NOs: 2 and 7 are disclosed. **In regard to the active fragment or derivative of a polynucleotide encoding CTGF-2 other than SEQ ID NO: 7, it is noted that the specification does not provide any disclosure whether these sequences from an active fragment or derivative of a polynucleotide encoding CTGF-2 would have had the same characteristics or properties** (see also 35 U.S.C. 112, second paragraph rejection above against claims 1-14 and 28-52 for indefiniteness).

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated: It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of a small genus such as a polynucleotide

encoding CTGF-2, a polynucleotide encoding CTGF-2, an active fragment or derivative thereof, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that **Applicant is in possession of an active fragment or derivative thereof of a polynucleotide encoding CTGF-2, besides SEQ ID NO: 7, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.**

Claims 1-14 and 28-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method of stimulating angiogenesis at the site of ischemia in a mammal, comprising the intramuscular administration of SEQ ID NO: 1, wherein SEQ ID NO: 1 is contained in adenoviral vector pTG14550, does not provide enablement for a method of stimulating angiogenesis in a mammal, comprising any route of administration of a polynucleotide encoding CTGF-2, wherein the mammal has restenosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1 is drawn to a method of stimulating angiogenesis in a mammal, comprising the administration of a polynucleotide encoding CTGF-2, or an active fragment or derivative thereof. Claims 12-14 and 28-52 are dependent on claim 1 and include all the limitations of claim 1, wherein the polynucleotide is contained in an adenoviral vector, wherein the mammal has

ischemia or restenosis, wherein the polynucleotide is delivered to the heart, wherein the polynucleotide is administered intramuscularly or intravenously, wherein the mammal is treated for limb revascularization, and wherein the polynucleotide is administered with a pharmaceutically acceptable carrier.

Human gene therapy is experimental and unpredictable. Anderson, WF (Nature, 1998 Vol. 392(6679 Suppl):25-30 assert that "except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease" (see page 25, first paragraph). Anderson also states, "several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered. The reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how *in vivo* immune defenses can be overcome, and how to manufacture efficiently the vectors that we do make. It is not surprising that we have not yet had notable clinical success" (see page 30, fifth paragraph).

Anderson, WF (Human Gene Therapy, 2002 Vol. 13:1261-1262) assert that the reason that gene therapy has been so long in coming is because successful gene therapy in human patients is much more complex than obtaining success in treating mice (see page 1261, first column, last paragraph).

Crystal, R. (Science, 1995 Vol. 270:404-410) points to the advantages of plasmid-containing complexes as gene transfer vectors, for instance, he also teaches that the disadvantages include general inefficiency at achieving successful gene transfer as well as a

general lack of available data regarding repetitive administration of DNA to whole organisms (see page 405, second paragraph).

Branch, A. (TIBS, February 1998 Vol. 23, pages 45-50) teach that the *in vivo* (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues (see page 49).

Applicants have not provided guidance in the specification toward a method of stimulating angiogenesis in a mammal, comprising any route of administration of a polynucleotide encoding CTGF-2, wherein the mammal has restenosis. While the instant invention specification provides methodologies for a method of stimulating angiogenesis at the site of ischemia in a mammal, comprising the intramuscular administration of SEQ ID NO: 1, wherein SEQ ID NO: 1 is contained in adenoviral vector pTG14550, the specification fails to teach the successful delivery of a polynucleotide encoding CTGF-2, other than SEQ ID NO: 1 and intramuscular administration (see also 35 U.S.C. 112, second paragraph rejection above against claims 1-14 and 28-52 for indefiniteness). It is unclear how the specific method of stimulating angiogenesis at the site of ischemia in a mammal, comprising the intramuscular administration of SEQ ID NO: 1, wherein SEQ ID NO: 1 is contained in adenoviral vector pTG14550 data is correlated with/or representative of a method of stimulating angiogenesis in a mammal, comprising any route of administration of a polynucleotide encoding CTGF-2, wherein the mammal has restenosis, where no specific guidance (i.e. specific mode of stimulation, delivery route, tissue specificity, etc.) is provided.

In view of the lack of guidance in the specification and known unpredictability associated with the *in vivo* delivery of nucleic acids as cited in the references of Anderson, 1998,

Anderson, 2002, Crystal, R., and Branch, A., one of ordinary skill in the art would require undue experimentation to practice the current invention. The quantity of experimentation required would include the sufficient systemic delivery of a polynucleotide encoding CTGF-2 to specific intracellular targets in quantities sufficient to stimulate angiogenesis in a mammal; the sustained and regulated expression of expression vectors comprising a polynucleotide encoding CTGF-2 in organ systems and cells in a mammal in a quantity that was sufficient to stimulate angiogenesis; and the design and delivery of an active fragment or derivative thereof of a polynucleotide encoding CTGF-2, such that angiogenesis would be stimulated. Therefore, undue experimentation would be required of a person of skill in the art to make and use the claimed invention, particularly, in view of the obstacles needed to overcome to use gene therapy methods as exemplified in the references discussed above. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Accordingly, limiting the scope of the claimed invention to a method of stimulating angiogenesis at the site of ischemia in a mammal, comprising the intramuscular administration of SEQ ID NO: 1, wherein SEQ ID NO: 1 is contained in adenoviral vector pTG14550 is proper.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 7, 9, 13, 31, and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Babic et al. (Proc. Natl. Acad. Sci., 1998 Vol. 95:6355-6360).

Claims 1 is drawn to a method of stimulating angiogenesis in a mammal, comprising the administration of a polynucleotide encoding CTGF-2, or an active fragment or derivative thereof. Claims 2, 7, 9, 13, 31, and 35 are dependent on claim 1 and include all the limitations of claim 1, wherein the polynucleotide is contained in an adenoviral vector, wherein the polynucleotide is administered intramuscularly, and wherein the polynucleotide is administered with a pharmaceutically acceptable carrier.

Babic et al. disclose that CYR61 (CTGF-2), promotes angiogenesis in a rat corneal pocket assay (see Abstract). Babic et al. further disclose that full length mouse CYR61 cDNA was constructed in pL61SN vector, administered into the rat cornea, and neovascularization was induced (see Figure 2 and Table 1).

Thus, Babic et al. anticipate claims 1, 2, 7, 9, 13, 31, and 35.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-8693 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
July 25, 2003

Karen Lacourciere

KAREN LACOURCIERE
PATENT EXAMINER